

## AMENDMENTS TO THE SPECIFICATION

Please replace section “DESCRIPTION OF THE FIGURES” (pages 8-9, followed by section entitled “DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS”) with the following:

### DESCRIPTION OF THE FIGURES

FIG. 1 shows the assay (using a quantitative RT-PCR method known to those practiced in the art) of the ataxin1 mRNA obtained from HEK293H cells that have been transfected with plasmid containing an anti-ataxin1 ribozyme (top lanes in FIG. 1) or with siRNA against ataxin1 (bottom lanes of FIG. 1).

FIG. 2 shows the assay (using the same quantitative RT-PCR method known to those practiced in the art) of the ataxin-1 mRNA obtained from HEK293H cells that have been transfected with anti-ataxin-1 small interfering RNA (bottom lanes) compared to the mRNA obtained from HEK293H cells that have been transfected with a control siRNA that targets the mRNA for glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

FIG. 3 shows the construction of the adeno-associated virus expression vector pAAV-siRNA.

FIG. 4 illustrates an investigational device (by Medtronic, Inc. of Minneapolis, Minn. Model 8506), which can be implanted subcutaneously on the cranium, and provides an access port through which therapeutic agents may be delivered to the brain.

FIG. 5 illustrates an investigational device (by Medtronic, Inc. of Minneapolis, Minn.--schematic of Model 8506), which can be implanted subcutaneously on the cranium, and provides an access port through which therapeutic agents may be delivered to the brain.

FIG. 6 illustrates the relation of various neurodegenerative diseases described herein, and the location of treatment with small interfering RNA vectors directed to their intended targeted gene product.

~~Figure 7 is a schematic side view depiction of a marker tip at the distal end of the catheter used in implementing the method of the invention.~~

**Please, replace section entitled “Devices” (Pages 28-30, followed by the section entitled “Examples”) with the following:**

## **Devices**

Using the small interfering RNA vectors previously described, the present invention also provides devices, systems, and methods for delivery of small interfering RNA to target locations of the brain. The envisioned route of delivery is through the use of implanted, indwelling, intraparenchymal catheters that provide a means for injecting small volumes of fluid containing AAV or other vectors directly into local brain tissue. The proximal end of these catheters may be connected to an implanted, intracerebral access port surgically affixed to the patient's cranium, or to an implanted drug pump located in the patient's torso.

Examples of the delivery devices within the scope of the present invention include the Model 8506 investigational device (by Medtronic, Inc. of Minneapolis, Minn.), which can be implanted subcutaneously on the cranium, and provides an access port through which therapeutic agents may be delivered to the brain. Delivery occurs through a stereotactically implanted polyurethane catheter. The Model 8506 is schematically depicted in FIGS. 4 and 5. Two models of catheters that can function with the Model 8506 access port include the Model 8770 ventricular catheter by Medtronic, Inc., for delivery to the intracerebral ventricles, which is disclosed in U.S. Pat. No. 6,093,180, incorporated herein by reference, and the IPA1 catheter by Medtronic, Inc., for delivery to the brain tissue itself (i.e., intraparenchymal delivery), disclosed in U.S. Ser. Nos. 09/540,444 and 09/625,751, which are incorporated herein by reference. The latter catheter has multiple outlets on its distal end to deliver the therapeutic agent to multiple sites along the catheter path. In addition to the aforementioned device, the delivery of the small interfering RNA vectors in accordance with the present invention can be accomplished with a wide variety of devices, including but not limited to U.S. Pat. Nos. 5,735,814, 5,814,014, and 6,042,579, all of which are incorporated herein by reference. Using the teachings of the present invention and those of skill in the art will recognize that these and other devices and systems may be suitable for delivery of small interfering RNA vectors for the treatment of neurodegenerative diseases in accordance with the present invention.

In one preferred embodiment, the method further comprises the steps of implanting a pump outside the brain, the pump coupled to a proximal end of the catheter, and operating the pump to deliver the predetermined dosage of the at least one small interfering RNA or small

interfering RNA vector through the discharge portion of the catheter. A further embodiment comprises the further step of periodically refreshing a supply of the at least one small interfering RNA or small interfering RNA vector to the pump outside said brain.

Thus, the present invention includes the delivery of small interfering RNA vectors using an implantable pump and catheter, like that taught in U.S. Pat. Nos. 5,735,814 and 6,042,579, and further using a sensor as part of the infusion system to regulate the amount of small interfering RNA vectors delivered to the brain, like that taught in U.S. Pat. No. 5,814,014. Other devices and systems can be used in accordance with the method of the present invention, for example, the devices and systems disclosed in U.S. Ser. No. 09/872,698 (filed Jun. 1, 2001) and Ser. No. 09/864,646 (filed May 23, 2001), which are incorporated herein by reference.

~~It is preferred to place some means for locating distal end 14 during the access and location process. This is preferably done by applying a marker 46, as shown in FIG. 7, to distal end 14 which is detected during the access and location process. If access and location is accomplished using some form of x-ray radiation, marker 46 is preferably radiopaque. Radiopaque marker 46 renders at least a portion of distal tip 14 opaque to x-rays, enabling the tip to be observed via fluoroscopy or via x-ray during access and location of catheter 10.~~

— In a preferred embodiment, radiopaque marker 46 comprises tantalum powder dispersed in a matrix composed of a biocompatible adhesive, such as those discussed above. Ordinarily, radiopaque marker 46 will be premolded prior to insertion into the lumen 38. After radiopaque marker 46 has been inserted into the lumen 38, a thin coating of the same biocompatible adhesive is preferably applied to the exterior of the hemispherical portion 48. Other materials may also be suitable for radiopaque marker 46, such as barium or platinum materials.

— Alternately, the radiographic marker 46 may be chosen of a material that has sufficient radiodensity for visualization during radiologic procedures, but in powdered form that is dispersed in the catheter tip at the time the catheter tip is molded.

— Alternatively, marker 46 may be composed of a material that is compatible to nuclear magnetic resonance imaging (MRI) to enable the tip to be detected during an MRI scan. Preferred material for such a marker 46 is platinum, though barium, tantalum, and similar materials are also suitable. Regardless of whether radiography or MRI is being utilized, the goal of providing a radiographic marker 46 is to enable the operator to accurately detect the precise

~~location of the tip to facilitate placement and later verification of the integrity and position of distal end 14 of catheter 10.~~

To summarize, the present invention provides methods to deliver small interfering RNA vectors to the human central nervous system, and thus treat neurodegenerative diseases by reducing the production of a pathogenic protein within neurons.

The present invention is directed for use as a treatment for neurodegenerative disorders and/or diseases, comprising Alzheimer's disease, Parkinson's disease, Huntington's disease, Spinocerebellar type 1, type 2, and type 3, and/or any neurodegenerative disease caused or aggravated by the production of a pathogenic protein, or any other neurodegenerative disease caused by the gain of a new, pathogenic function by a mutant protein.